**Note to reader: This report contains a reevaluation and revision of the uncertainty factors and, therefore, supercedes previous report dated January 13 2004. (TXR No. 0052291).**

**TXR NO. 0052467**

**DATE: April 2, 2004**

**MEMORANDUM**

**SUBJECT:** ***Metam Sodium (039003), Metam Potassium (039002), Dazomet (035602), and MITC (068103)*** 2nd Joint Report of the Hazard Identification Assessment Review Committee.

**FROM:** Anna Lowit
Reregistration Branch 2
Health Effects Division (7509C)

**THROUGH:** Jess Rowland, Co-Chair
and
Karen Whitby, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

**TO:** Carol Christensen, Risk Assessor
Reregistration Branch 2
Health Effects Division (7509C)

PC Codes: 035602, 068103, 039003 and 039002

The Hazard Identification Assessment Review Committee (HIARC) of the Health Effects Division (HED) reviewed metam sodium, metam potassium, dazomet, and methylisothiocyanate (MITC; TXR nos. 014062, 0050766, 0050765, 052226, 0052291), most recently on January 23, 2003, June 5, 2003, and March 16, 2004. Metam sodium, metam potassium, dazomet, and MITC are each registered as fumigants. At present time, no dietary exposure is expected for these pesticides. Therefore, they are evaluated for risk assessment as 'non-food-use' chemicals and are not subject to the Food Quality Protection Act (FQPA) of 1996. Previous HIARC

reviews have evaluated these chemicals as 'food use' chemicals and therefore subject to consideration under the FQPA. The toxicology and exposure profiles of metam sodium, metam potassium, and dazomet are interrelated. Specifically, metam sodium, metam potassium, and dazomet are considered carriers of MITC since they convert to MITC quickly under environmental conditions. Metam sodium metam potassium, and dazomet are also metabolized *in vivo* to MITC. Therefore, these pesticides are reviewed in a single hazard identification report. The current report provides the hazard identification, uncertainty factor determination, and hazard characterization from the January 23, 2003, June 5, 2003, and March 16, 2004 meetings for only those exposure scenarios which will be considered in the quantitative risk assessment.

Committee Members in Attendance at the March 16, 2004 Meeting

Members present were: Ayaad Assaad, William Burnam, Jonathan Chen, Bill Dykstra, Paula Deschamp, Ray Kent, Jessica Kidwell, John Liccione, Susan Makris, Elizabeth Mendez, PV Shah, Jess Rowland, Karen Whitby

Member(s) in absentia: None

Data evaluation prepared by: Anna Lowit, RRB2

Also in attendance were: Vicki Dellarco, Mike Metzger, Pauline Wagner, Veronique LaCapra (SRRD), Jeff Herndon, Steven Weiss, Judy Facey, Carol Christensen

Committee Members in Attendance at the June 5, 2003 Meeting

Members present were: Ayaad Assaad, William Burnam, Jonathan Chen, Paula Deschamp, Pamela Hurley, John Liccione, Susan Makris, Elizabeth Mendez, PV Shah, Jess Rowland, Brenda Tarplee,

Member(s) in absentia: None

Data evaluation prepared by: Anna Lowit, RRB2

Also in attendance were: Pauline Wagner, Veronique LaCapra (SRRD), Ken Dockter, Steven Weiss, Judy Facey, Carol Christensen, Sherrie Kinard

Committee Members in Attendance at the January 23, 2003 Meeting

Members present were: Ayaad Assaad, William Burnam, Jonathan Chen, Paula Deschamp, Elizabeth Doyle, Pamela Hurley, John Liccione, Susan Makris, David Nixon, Bill Dykstra, PV Shah, Jess Rowland, Brenda Tarplee,

Member(s) in absentia: None

Data evaluation prepared by: Anna Lowit, RRB2

Also in attendance were: Pauline Wagner, Veronique LaCapra (SRRD), Ken Dockter, Steven Weiss, Judy Facey, Carol Christensen, Sherrie Kinard, Alan Levy, Bill Sette, Maria Rodriquez (RD), Tim McMahon (AD)

Data Evaluation / Report Presentation

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Anna Lowit
Toxicologist

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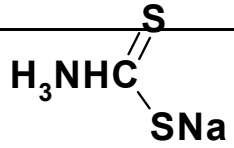
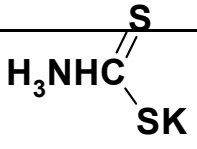
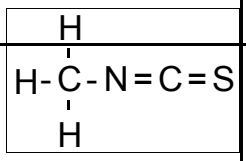
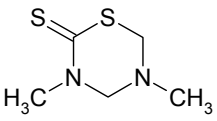
## I. INTRODUCTION

The Hazard Identification Assessment Review Committee (HIARC) of the Health Effects Division (HED) have reviewed metam sodium, metam potassium, dazomet, and methylisothiocyanate (MITC; TXR nos. 014062, 0050766, 0050765, 052226, 0052291), most recently on January 23, 2003, June 5, 2003, and March 16, 2004. Metam sodium, metam potassium, dazomet, and MITC are each registered as fumigants. At present time, no dietary exposure is expected for these pesticides. Therefore, they are evaluated for risk assessment as 'non-food-use' chemicals and are not subject to the Food Quality Protection Act (FQPA) of 1996. Previous HIARC reviews have evaluated these chemicals as 'food use' chemicals and therefore subject to consideration under the FQPA. The toxicology and exposure profiles of metam sodium, metam potassium, and dazomet are interrelated. Specifically, metam sodium, metam potassium, and dazomet are considered carriers of MITC since they convert to MITC quickly under environmental conditions. Metam sodium, metam potassium, and dazomet are metabolized *in vivo* to MITC. Therefore, these pesticides are reviewed in a single hazard identification report. The current report provides the hazard identification, uncertainty factor determination, and hazard characterization from the January 23, 2003, June 5, 2003, and March 16, 2004 meetings only for those exposure scenarios which will be considered in the quantitative risk assessment. At present time, HED and AD plan to use a common set of hazard endpoints in their exposure assessments of these chemicals. Metam sodium and metam potassium are both extremely soluble in water and differ only by their cation; HED has previously accepted toxicity data for metam sodium for the registration of metam potassium. All endpoints and uncertainty factors selected for metam sodium also apply to metam potassium.

Metam sodium, metam potassium, and dazomet are used as agricultural fumigants to control weeds, nematodes, and fungi on a variety of crops. Although dazomet can also be used as a pre-plant soil fumigant before planting residential lawns, no residential exposure to MITC or dazomet is expected. MITC is registered as an active ingredient for sterilizing treated wood products (e.g., telephone poles). Metam potassium is also used in sugarcane processing plants to clean process equipment; no residues of metam potassium or MITC are expected in sugar. Based on pounds of active ingredient used, metam sodium is the third most widely used agricultural pesticide in the US. However, due to off-gassing of MITC from the soil, no residues of metam sodium or MITC are expected in treated commodities. The primary pathway of exposure from the use of these chemicals is inhalation exposure to MITC in ambient air.

There are several toxicologically notable metabolites/degradates: methyl isocyanate (MIC), carbon disulfide ($CS_2$) and hydrogen sulfide ($H_2S$). Specifically, methyl isocyanate (MIC) is a photolysis degradate of the MITC which has been measured in ambient air around agricultural areas of California. Following soil application of metam sodium or metam potassium, both $CS_2$ and $H_2S$ can be formed; the relative amounts depend on the pH of the soil. Following oral exposure to metam sodium and dazomet, rats metabolize approximately 20% and 2%, respectively, of the dose (on a molar basis) to $CS_2$. Studies conducted with MIC, $CS_2$, and $H_2S$ were considered at the January 23, 2003 HIARC meeting (TXR no. 0052291). Toxicological profiles and hazard identification for carbon disulfide ($CS_2$) and hydrogen sulfide ($H_2S$) are available on EPA's Integrated Risk Information System (IRIS) database. This information is summarized in the Revised Toxicology Disciplinary Chapter for Metam Sodium and MITC (TXR no. 0052455). Information on the toxicity of methylisocyanate is also summarized in the revised toxicology chapter.

| Table 1. Structures and molar equivalents for metam sodium, metam potassium, MITC, and dazomet. | | | | |
|---|---|---|---|---|
| | **Metam Sodium** | **Metam Potassium** | **MITC** | **Dazomet** |
| **Structure** |  |  |  |  |
| **CAS No.** | 137-42-8 | 137-41-7 | 556-61-6 | 533-74-4 |
| **MITC Molar Equivalents** | 0.56 | 0.50 | 1 | 0.45 |
| **Molecular weight** | 129.18 | 145.27 | 73.12 | 162.27 |

## II. EXTRAPOLATION AND UNCERTAINTY FACTORS

The current report provides the hazard identification and uncertainty factor determination from the January 23, 2003, June 5, 2003, and March 16, 2004 meetings for those exposure scenarios which will be considered in the quantitative risk assessment.

### 1. Default Inter- and Intra-Species Extrapolation Factors

The default 10x factors for inter- and intra-species extrapolation should be applied to the toxicological endpoints selected from studies with laboratory animals (total = 100x).

### 2. Database Uncertainty Factor

The database of toxicology studies for metam sodium and dazomet are complete for risk assessment purposes. The database for MITC, however, is incomplete. Many toxicological studies via the oral route with MITC do not meet the guideline requirements, primarily due to problems surrounding the volatility of MITC and inadequate characterization of exposure concentrations or doses. Some of the data gaps are being filled through bridging with the toxicology databases of metam sodium and

dazomet. Specifically, for evaluating the sensitivity and susceptibility of infants and children, the HIARC has previously concluded that oral dazomet developmental and reproductive toxicity studies can serve as a surrogate for MITC. Because of inadequate dosing in the oral chronic/carcinogenicity studies in mice and rats, the oral MITC studies are considered inadequate for evaluating carcinogenic potential. The Q-1* for metam sodium (adjusted by molar conversion to MITC) has been used for quantitative cancer risk assessment to MITC.

There is remarkable similarity in the doses causing similar toxic effects for metam sodium, dazomet, and MITC, particularly at low to moderate doses. Specifically, reduced body weight gain and food consumption in addition to changes in hematological parameters were observed at low doses in oral toxicity studies with rats, mice, rabbits, and dogs. Effects on the liver have been noted in dogs at doses with similar molar levels. Reduced motor activity has been noted at all dose levels in oral acute neurotoxicity testing in studies with metam sodium and dazomet. In oral developmental toxicity studies with MITC, dazomet, and metam sodium, effects such as fetal weight decrement, reduced ossification of various skeletal structures, and increased incidence of resorptions have been noted at similar molar dose levels. EPA has in hand a human study of eye irritation with MITC (MRID 44400401). This study is still under review, and, until that review is completed, will not be considered in selecting endpoints for purposes of quantitative risk assessment. OPP expects to complete its review shortly, and may then reconsider the conclusions in this HIARC document.

Several additional studies are required for MITC:

1. *Acute neurotoxicity study in rat via inhalation with pathological evaluation of the complete respiratory tract.* This study is expected to characterize the acute or single day inhalation exposures to MITC that are typical for this chemical. The neurotoxicity component will be used verify the effects on motor activity observed in single oral studies with both dazomet and metam sodium. The pathological evaluation of the respiratory tract will help characterize the impact of port-of-entry effects (as seen in the 28-day inhalation study with MITC and 90-day inhalation study with metam sodium) for this highly irritating compound and to help characterize the eye irritation observed for 1-8 hours in humans (MRID 44400401).

2. *Two generation reproduction study in rat via inhalation with pathological evaluation of the complete respiratory tract.* This study should also include a subchronic neurotoxicity component with functional battery and motor activity measurements using the F0 animals. If the F1 animals exhibit developmental neurotoxicity then the F2 generation should be evaluated for the standard developmental neurotoxicity parameters. This study will help characterize exposure to MITC in ambient air, particularly pregnant rats and their pups. It also notable that developmental effects such as pup death and survivability were observed in inhalation developmental toxicity studies with MIC, a photolysis degradate of MITC.

3. *In vivo cytogenetic assay*: See Section V.

4. *Repeat of the unscheduled DNA synthesis assay*: See Section V.

These studies are expected to provide additional characterization, particulary for the port-of-entry effects. **At this time, an additional database uncertainty factor is not necessary.**

### 3. NOAEL to LOAEL Extrapolation Factor

A NOAEL to LOAEL uncertainty factor (10x) should be applied to the short-term dermal endpoint for dermal exposure to dazomet only. The LOAEL of 15 mg/kg is based on neurobehavioral effects in females (reduced number of rearings and decreased motor activity) and was observed in the acute neurotoxicity study with dazomet. No NOAEL was identified in this study.

### 4. Other Factors

As discussed above at present time, no dietary exposure is expected for metam sodium, MITC, and dazomet. **These chemicals are not subject to the FQPA (1996); therefore, the FQPA 10x Factor does not apply**. However, previously, when evaluated as food-used chemicals (May 21, 2002, January 23, 2003 and June 5, 2003), the HIARC determined that the special FQPA Safety Factors could be removed (**1x** ) for metam sodium, MITC, and dazomet. [If evaluated as food-used chemicals in the future, the reader is referred to TXR no. 0052291]

## III. TOXICITY ENDPOINT SELECTION

### 1. Acute and Chronic Reference Dose (aRfD/cRfD)

Dietary exposure to metam sodium, metam potassium, dazomet, and/or MITC is not expected. Acute and chronic reference doses are not necessary at this time.

### 2. Incidental Oral Exposure-Short- and Intermediate-Term (1-30 days, 1-6 months)

Based on the physical chemical properties and the use pattern of these chemicals, incidental oral exposure to infants and children are not expected for metam sodium, metam potassium, dazomet, and MITC.

### 3. Dermal Absorption

#### a. Metam Sodium

Dermal Absorption Factor: 2.5%

$^{14}$C-Metam sodium was applied to male rats in aqueous formulations at the nominal dose levels of 0.1, 1 and 10 mg/rat to an area of 11.6 $cm^2$ on the back. The application site was protected by a glass saddle which contained an activated charcoal filter to adsorb any volatile radioactivity which evaporated from the skin surface. Within each group, four animals were killed following a 1, 2, 10, and 24 hours exposure and excreta collected over the study period, For 4 additional animals in each treatment group, the treatment area was washed 10 h after administration and excretion monitored over a total of 72 hours. Mean percent absorbed dose at 10 hours was 2.5% (2.355%, 3.683%, 1.514%, respectively).

**b. MITC**

No dermal absorption studies are available. The HIARC did not select a dermal absorption factor for MITC. Dermal endpoints were not selected; dermal risk assessments for MITC are not required.

**c. Dazomet**

Dermal Absorption Factor: 4.5%

No dermal absorption studies are available. A percent dermal absorption can be estimated by comparing the results of the oral and dermal toxicity studies. Ideally, LOAEL for the similar effects and in the same species via oral and dermal route may be used in estimating dermal absorption. However, the NOAEL in rabbit 21-day dermal toxicity were greater than 1000 mg/kg/day (HDT). A dermal absorption value for Dazomet is estimated to be 4.5% (developmental and maternal LOAEL of 45 mg/kg/day in rabbits divided by NOAEL of 1000 mg/kg/day dermal study times 100). The HIARC selected a dermal absorption value of 4.5% as an upper bound estimate.

**4. Short- Term, Dermal (1-30 days) Exposure**

**a. Metam Sodium**

Study Selected: Developmental toxicity study in rat (**Metam sodium**) § N/A

MRID Nos.: 41577101, 42170101, and 92097012

Executive Summary: In a developmental toxicity study (MRIDs 41577101, 42170101, and 92097012) **metam sodium** 42.2%) was administered at dose levels of 0, 4.22, 16.88, and 50.64 mg/kg/day by gavage to pregnant Wistar rats from days 6 through 15 of gestation (GD). On GD 20, all dams were sacrificed and necropsied, and all fetuses were weighted, sexed, and examined externally for abnormalities.

Maternal toxicity was observed at 16.88 and 50.64 mg/kg/day levels as significantly decreased body weight gain during the dosing period. The corrected maternal body weight gain was significantly reduced (-22% vs. control) at 50.64 mg/kg/day. Although not statistically analyzed, mean maternal feed consumption was reduced during the treatment period. The greatest decrease occurred initially, days 7-8 for the 16.88 and the 50.64 mg/kg/day groups (-16% and -19% vs. control, respectively).

The cesarean section data indicate a significant increase in postimplantation loss (↑146% and ↑103%) and a significant decrease in the % of live fetuses/dam (-11.4% and -8%) at the 4.22 and 50.64 mg/kg/day levels, respectively. However, because of the lack of a similar effect at the mid dose, there is no dose-response. Fetal weights were significantly reduced for male and female fetuses in the 50.64 mg/kg/day group (-7% and -8% vs. control, respectively). Examination of the viscera of fetuses that underwent skeletal examination revealed a significant increase in the % fetuses/litter with anomalies, variations, and retardations at the 16.88 mg/kg/day level, which were dose-related (except for anomalies). There were significant increases in the % fetuses/litter with variations and retardations at the 50.64 mg/kg/day level which were dose-related. Meningocele was noted in 2 fetuses (0.51% of the fetuses examined per litter) in 1 litter (4.55% of litters) at the 50.64 mg/kg/day group.

**The maternal LOAEL is 16.88 mg/kg bw/day (9.45 mg/kg/day MITC equiv.), based on reduced body weight gain and decreased food efficiency. The maternal NOAEL is 4.22 mg/kg bw/day (2.36 mg/kg/day MITC equiv.).**

**The developmental LOAEL is 16.88 mg/kg bw/day (9.45 mg/kg/day MITC equiv.), based on the increased incidence of skeletal observations and the increase in total resorptions and resorptions/dam The developmental NOAEL is 4.22 mg/kg /day (2.36 mg/kg/day MITC equiv.).**

The developmental toxicity study in the rat is classified **acceptable-guideline** and **satisfies** the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

Dose and Endpoint for Risk Assessment: NOAEL of 4.22 mg/kg/day based on the increased incidence of skeletal observations at 16.88 mg/kg/day

Comments about Study/Margins of Exposure: In the metam sodium dermal study (MRID no. 41106204), the systemic NOAEL is approximately 125 mg/kg/day (highest dose tested). Local erythema, edema, and dermatitis at 62.5 mg/kg/day were noted in the metam sodium dermal study. An aqueous solution was used; therefore MITC is expected to be formed immediately and volatilize within an hour since the dosing site was not covered. The dose of 4.22 mg/kg/day selected would address the concern for developmental toxicity which was seen in the presence of maternal toxicity at the same dose. Since an oral NOAEL was selected, the 2.5 % dermal absorption factor should be used for route-to-route extrapolation.

**b. MITC**

Study Selected: The HIARC did not select a short-term dermal endpoint for MITC. No dermal hazard via typical dermal contact with MITC is expected. Unprotected skin could be exposed to MITC vapor; however this exposure can not, at this time, be quantified.

**c. Dazomet**

Study: Acute Neurotoxicity Study with *Dazomet* § 81-8

MRID No.: 43465302

Executive Summary: In an acute neurotoxicity study (MRID # 43465302), Wistar Chbb: THOM (SPF) rats (10/sex/group) were orally gavaged once with **dazomet** in 0.5% aqueous carboxymethylcellulose at doses of 0 (vehicle only), 50, 150 and 450 mg/kg body weight (a.i. equivalents: 50, 130, and 450 mg/kg) for males and 0, 15, 50, and 150 mg/kg body weight (a.i. equivalents: 13, 50, and 130 mg/kg) for females. The animals were observed for mortality and clinical signs of toxicity for 14 days post-dosing. Compound-related decreases in body weight were noted in mid-(7.0%) and high-(12.7%) dose males at day 7; the body weight gains for the same dose groups were 34.2% and 58.6%, respectively. A dose-dependent increase in clinical signs (half closure of eyelids, salivation, lacrimation, impaired activity in open field, changes in fur, reduced number of rearings) and impairment of motor activity was seen in males and/or females at all dose levels. These effects were reversible by observation Day 7. No treatment-related gross or neuropathological findings were present.

**The NOAEL for systemic toxicity with *dazomet* is 50 mg/kg in males (22.5 mg/kg MITC equivalents) not established (>HDT) in females. The LOAEL for systemic toxicity with *dazomet* is 150 mg/kg in males (67.5 mg/kg MITC equivalents) based on decreased body weight and body weight gain.**

**Based on the findings of this study (screening battery), the LOAELs with *dazomet* for neurobehavioral effects were established at 50 mg/kg in males (22.5 mg/kg MITC equivalents; FOB findings and reduced number of rearings) and 15 mg/kg in females (6.75 mg/kg MITC equivalents; decreased motor activity).**

The study is classified as **acceptable-guideline** and **satisfies** the requirements (81-8) for an acute neurotoxicity in rats.

Dose and Endpoint for Risk Assessment: LOAEL = 15 mg/kg based on neurobehavioral effects in females (reduced number of rearings and decreased motor activity). A NOAEL was not achieved.

Comments about Study/Endpoint/MOE: The assumption is made that a similar metabolic pathway exists via the oral and dermal route. The neurobehavioral effects seen in the acute neurotoxicity study, are generally not evaluated in 21-day dermal toxicity study, therefore, acute neurotoxicity study in rats is recommended for this risk assessment. An additional **10x** uncertainty factor is required for the use of a LOAEL ($UF_L$). Since an oral

LOAEL was selected, the 4.5 % dermal absorption factor should be used for route-to-route extrapolation.

The HIARC previously considered the BASF request to use 21 day dermal toxicity study in rabbits for short-term dermal exposure risk assessment. However, the HIARC concluded that this study is not suitable for short-term dermal exposure risk assessment because of the neurobehavioral effects seen in both males and female rats in the acute neurotoxicity study (MRID 43465302) in rats. If the registrant prefers that the HIARC consider a dermal study for this risk assessment, then this study should include neurotoxicity evaluations and should be conducted in rats since the rabbit is generally considered as a poor model for evaluation of neurotoxic effects.

**5. Intermediate- Term, Dermal (1 -6 months) Exposure**

**a. Metam Sodium**

Study Selected: Chronic toxicity in the dog (**Metam sodium**) §83-1b

MRID No.: 43275801

Executive Summary: In a chronic toxicity study (MRID # 43275801), metam sodium (43.148% w/w, Batch Reference: BAS/005/00N 90-2) was administered to 4 beagle dogs/sex/dose in gelatin capsules at doses of 0, 0.05, 0.1, and 1.0 mg/kg/day (0, 0.028, 0.056 and 0.56 mg/kg/day MITC equivalent) for 52 weeks. The study was conducted in two randomized blocks, each comprising two male and two female replicates consisting of one dog per treatment group.

There were no deaths nor treatment-related clinical signs of toxicity. Group mean body weights of the treated animals were comparable to the control group over the course of the study, except for a decrease of 1.5% at week 4 in a male dog at the 0.1 mg/kg/day dose level. There was also a decrease of 9% at week 50 in a female dog at the 0.1 mg/kg/day dose level.

Statistically significant increases in kaolin-cephalin time at the 1.0 mg/kg/day dose level were observed at week 4 (6%), week 13 (7%) and week 26 (10%) in male dogs. Increase in kaolin-cephalin time at the 1.0 mg/kg/day dose level was also observed in female dogs at week 4 (13%), week 13 (7%) and week 52 (9%). A statistical significant increase (92%) was also note in monocyte count for male dogs at week 13 at all dose levels. There was an increase of 56% compared to control in eosinophil count in male dogs at the 0.05 mg/kg/day dose level at week 13.

Group mean ALT levels at 1.0 mg/kg/day gradually increased in female dogs over the course of the study until study termination, where the mean value was 3x control. However, the increase was due to changes in one female dog whose ALT level spiked during weeks 45 and 52. This animal also had a 15% increase in AST compared to control. Increase in AST was noted in male dogs at week 13 at the 0.05 mg/kg/day

(22%) and 0.1 mg/kg/day (30%), and week 52 at the 0.05 mg/kg/day (15%). Increase in AST was also observed in female dogs at week 52 at the 1.0 mg/kg/day (23%).

The only treatment related finding in necropsy was on microscopic examination of the liver of the female from the 1 mg/kg/day dose group with ALT elevation. This animal had a slight increase in hepatocyte and macrophage/Kupffer cell pigmentation, slight mononuclear cell infiltration, slight telangiectasis, and a positive reaction for hemosiderin. However, one control group female also had hepatic changes consisting of monocellular infiltration, minimal hepatocyte pigmentation and increased macrophage/ Kupffer cell pigmentation.

**The LOAEL is > 1mg/kg/day (>0.56 mg/kg/day MITC equi.) in males and equal to 1 mg/kg/day (0.56 mg/kg/day MITC equi.) for females, based on increased ALT and microscopic changes in the liver. The NOAEL is = 1 mg/kg/day (0.56 mg/kg/day MITC equi.) for males and 0.1 mg/kg/day (0.056 mg/kg/day MITC equi.) for females.**

This chronic study in the dog is **acceptable-guideline** and satisfies the guideline requirement for a chronic oral study [OPPTS 870.4100, OECD 452] in dog. The registrant reported that the changes seen in the liver were of a similar nature to those observed in previous studies with this compound in dogs but of a reduced severity.

Dose and Endpoint for Risk Assessment: The NOAEL of 0.1 mg/kg/day is based on increased ALT and microscopic changes in the liver observed in female dogs at 1 mg/kg/day. This dose/endpoint is appropriate for the intermediate-term exposure duration since increases in ALT were seen over the course over the study until termination.

Comments about Study/Endpoint: In the metam sodium dermal study (MRID no. 41106204), the systemic NOAEL is approximately 125 mg/kg/day (highest dose tested). Local erythema, edema, and dermatitis at 62.5 mg/kg/day were noted in the metam sodium dermal study. An aqueous solution was used; therefore MITC is expected to be formed immediately and volatilize within an hour since the dosing site was not covered. Since an oral NOAEL was selected, the 2.5 % dermal absorption factor should be used for route-to-route extrapolation.

**b. MITC**

Study Selected: The HIARC did not select a intermediate-term dermal endpoint for MITC. No dermal hazard via typical dermal contact with MITC is expected. Unprotected skin could be exposed to MITC vapor; however this exposure can not, at this time, be quantified.

**c. Dazomet**

Study Selected: Subchronic Toxicity- Feeding Rats §82-1

MRID No.: 41865502

Executive Summary: In a subchronic toxicity study (MRID 41865502), dazomet(>97% a.i.) was administered to 10 Wistar Chub-THOM (SPF) rats/sex/dose in the diet for 90 days, at dose levels of 0, 20, 60, 180, or 360 ppm. The dose of 20 ppm (**30** ppm achieved intake in males [**1.5** mg/kg/day]; **34** ppm achieved intake in females [**1.7** mg/kg/day]) 60 ppm (**90** ppm achieved intake in males [**4.5** mg/kg/day]; **106** ppm achieved intake in females [**5.3** mg/kg/day]), 180 ppm (**274** ppm achieved intake in males [**13.7** mg/kg/day]; **308** ppm achieved intake in females [**15.4** mg/kg/day]) and 360 ppm (**560** ppm achieved intake in males [**28.0** mg/kg/day]; **640** ppm achieved intake in females [**32** mg/kg/day]).

No mortality or clinical toxicity was observed in male or female rats over the course of this study. Overall body weight gain in the 360 ppm dose groups of male and female rats was decreased by 13% and 26%, respectively vs controls for the study duration. Body weight was not affected in male or female rats at any other dose level. Statistically significant decreases in serum total protein and albumin were observed at the 60 ppm, 180 ppm, and 360 ppm dose level in male and female rats, but was apparently treatment related only in female rats (based on historical controls data). Increased absolute liver weight and liver:body weight ratio was observed in male rats from the 60, 180, and 360 ppm dose levels. Increased liver:body weight ratio was observed in female rats at the 180 and 360 ppm dose levels. Alterations in clinical pathology observed in this study were minimal and were confined to the 360 ppm dose level. At this dose, significant decreases in hemoglobin were reported for male and female rats at study termination.

Based upon the results of this study, the **systemic NOAEL is = 20 ppm (achieved intake of 1.5 and 1.7 mg/kg/day male and female rats, respectively). The systemic LOAEL is = 60 ppm (achieved intake of 4.5 mg/kg/day) for male rats** based on increased liver weight, liver:body weight ratio and pronounced foci of fatty degeneration in the liver. The **systemic LOAEL = 180 ppm (achieved intake of 15.4 mg/kg/day) for female rats** based on increased liver:body weight ratio and pronounced foci of fatty degeneration in the liver.

This study is classified as **Acceptable/Guideline** and **satisfies** the guideline requirement for a subchronic oral study (82-1) in the rats.

Dose/Endpoint for Risk Assessment: NOAEL = 1.5 mg/kg/day for male rats based on increased liver weight, liver:body weight ratio and pronounced foci of fatty degeneration in the liver at 4.5 mg/kg/day.

Comments about Study/Endpoint: This study is suitable for intermediate exposure: 1) time period of the study is similar to the intermediate term exposure pattern, and 2) a 90 day dermal toxicity study is not available. The effects seen in male rats (increased liver weight, liver:body weight ratio and pronounced foci of fatty degeneration in the liver) are presumed to occur via dermal route. Since an oral NOAEL was selected, the 4.5 % dermal absorption factor should be used for route-to-route extrapolation.

## 6. Long-Term Dermal (>6 Months) Exposure

### a. Metam Sodium

Study Selected: Chronic dog in Metam sodium

Executive Summary: See above for intermediate-term dermal exposure

Dose and Endpoint for Risk Assessment: See above for intermediate-term dermal exposure

Comments about Study/Endpoint: See above for intermediate-term dermal exposure

### b. MITC

Study Selected: The HIARC did not select a long-term dermal endpoint for MITC. No dermal hazard via typical dermal contact with MITC is expected. Unprotected skin could be exposed to MITC vapor; however this exposure can not, at this time, be quantified.

### c. Dazomet

Study Selected: The HIARC did not select a long-term dermal endpoint for dazomet. Long-Term exposure via the dermal route is not expected considering the use pattern and its stability in the environment.

## 7. Short-term (1-30 days), and Intermediate-term (1-6 months) Inhalation Exposure

### a. Metam Sodium

Study Selected: 90-Day Inhalation Study (**Metam sodium**) § 82-4

MRID No.: 00162041

Executive Summary: In a 90-day inhalation (MRID no. 00162041), 18 Sprague-Dawley rats/sex/dose group were exposed to aerosolized **metam sodium** (37% a.i.) in whole-body chambers for 6 hr/day, 5 days/week. The cumulative mean chamber metam sodium concentrations were 0, 6.5, 45 and 160 mg/$m^3$ (measured values based on the *sodium ion* level corrected for sodium ion levels measured from the control). Reviewers at the California Department of Pesticide Regulation calculated the doses to be 0, 1.11, 7.71, and 27.43 mg/kg/day. Mean MITC measured concentrations were 0, 0.78, 2.2, and 5.7 mg/$m^3$ (0, 0.12, 0.38, 0.98 mg/kg/day) (measured by infrared adsorption).

Clinical signs of salivation, dullness, chromodacryorhea, dehydration, rough coat, and wet coat were noted in males and females of the highest concentration level. There were no treatment related mortalities.

Body weight gain was reduced at the highest concentration level compared to control (-

6% and -8% for males and females). Food consumption was decreased compared to control in the mid and highest levels (-8% and -10%).

At the interim measurement, plasma lactate dehydrogenase levels were statistically reduced by 50% and 62% ($p< 0.05$) in females in the mid and high dose levels compared to control but only the highest dose in males (-18%). At termination, albumin was decreased compared to control (-13% and -22%; $p<0.05$) and alkaline phosphatase increased (+2-fold; $p<0.05$) at the mid and high dose levels in females only.

Although the absolute weights were not affected, significant increases in relative lung (+13% males, +21% females) and kidney (+7% males, +14% females) weights were noted in the highest dose group.

Histopathology indicative of irritation was noted in the nasal passages, lung, and stomach. A dose-dependant increase in the incidence of mucigenic hyperplasia of the nasal passage was noted in all treatment groups for females but only reached statistical significance in the mid and high dose group. This finding (ie, incidence of mucigenic hyperplasia) was increased ($p<0.05$) in the male high dose group. Mucigenic cysts were noted in 2 females of the highest dose group. A dose-dependant increase in lymphocytic rhinitis was noted in all treatment groups although statistical significance was noted only at the mid and high dose males. In the lungs, histiocytosis was noted in 3/27 high dose males and 2/18 high dose females. In the stomach, erosive gastritus was statistically increased in the high dose males and females (9/17 males, 13/18 females). Ulcerative gastritis was noted in 2/18 high dose females. Gross pathological changes in the stomach were also noted at the high dose in males and females by in an increased incidence in red/black foci or streaks. (It is notable that based on the incidence of stomach lesions, some oral ingestion from licking the fur has likely occurred in the whole body chambers.)

**The LOAEL in females is 45 mg/m$^3$ (7.71 mg/kg/day)of *metam sodium* (based on Na levels; 2.2 mg/m$^3$ [0.38 mg/kg/day] measured MITC), based on histopathological changes in the naval passages (ie, mucigenic hyperplasia) and changes in clinical chemistry. The LOAEL in males is 160 mg/m$^3$ (27.43 mg/kg/day) of *metam sodium* (based on Na levels; 5.7 mg/m$^3$ [0.98 mg/kg/day]) based on histopathological changes in the lungs and nasal passages.**

**The NOAEL for females is 6.5 mg/m$^3$ (1.11 mg/kg/day)of *metam sodium* (based on Na levels; 0.7 mg/m$^3$ [0.12 mg/kg/day] measured MITC). The NOAEL for males is 45 mg/m$^3$ (7.71 mg/kg/day)of *metam sodium* (based on Na levels; 2.2 mg/m$^3$ [0.38 mg/kg/day] measured MITC).**

This subchronic inhalation toxicity study in the rat is **acceptable-guideline** and satisfies the guideline requirement for a subchronic inhalation study OPPTS 870.3465; OECD 413 in the rat

Dose/Endpoint for Risk Assessment: The NOAEL for females is 6.5 mg/m$^3$ (**1.11**

**mg/kg/day**) of metam sodium (based on Na levels; 0.7 mg/m$^3$ [0.12 mg/kg/day] measured MITC). The LOAEL in females is 45 mg/m$^3$ (7.71 mg/kg/day) of metam

sodium (based on Na levels; 2.2 mg/m$^3$ [0.38 mg/kg/day] measured MITC), based on histopathological changes in the nasal passages (ie, mucigenic hyperplasia) and changes in clinical chemistry.

Comments about Study/Margins of Exposure: When metam sodium is applied to an agricultural field $CS_2$, $H_2S$, and MIC are formed in addition to MITC. Although the other gases were not measured, due to the rapid degradation of metam sodium, it is assumed that these compounds are also present in the inhalation chamber. Use of this study more accurately reflects the mixture of chemicals that people are actually exposed to, particularly in the field. Finally, the when adjusted for molar equivalents, NOAEL from metam sodium inhalation study is protective of the NOAELs identified for use in the inhalation RfC identified in EPA's IRIS database for $CS_2$ and $H_2S$ (19.7 mg/m$^3$ and 1.01 mg/m$^3$, respectively).

**b. MITC**

Study Selected: Subchronic Inhalation Toxicity-Rat § 82-4

MRID No.: 45314802

Executive Summary: In a 28 day inhalation toxicity study (MRID 45314802), Methyl Isothiocyanate [96.9 % a.i.] was administered to 5/sex/dose of SPF Wistar/Chubb:THOM rats by whole body exposure at analytical concentrations of 0, 5.0, 20, or 100 mg/m$^3$ equivalent to 0, 5.0, 20, or 100 ug/L(measured concentrations 0, 5.1, 19.9 or 100 ug/L) for 6 hours per day, 5 days/week for a total of 28 days.

All animals survived to study termination. Mid and high dose rats demonstrated clinical signs during exposure from the third exposure period onward. In the high dose rats, the signs persisted during the non-exposure periods. Body weight and body weight gain were significantly decreased ($p<0.05$) at the high dose. Food consumption and feed efficiency were not measured. There was an increase in serum bilirubin that was statistically significant ($p<0.01$) in the high dose males. The biological significance of the increase is unknown. There was increased lung weight, accompanied by bronchopneumonia, as well as other gross and microscopic changes in the respiratory tract of high dose male and female rats including, but not limited to, atrophy of the olfactory epithelium; tracheal cell necrosis, and focal squamous cell metaplasia in the respiratory epithelium.

**The LOAEL is 100 mg/m$^3$, based on persistent clinical signs, body weight changes, and gross and histopathological lesions observed in the high dose rats. The NOAEL is 20 mg/m$^3$.**

This subchronic toxicity study is **Acceptable but does not satisfy** the guideline requirement for a subchronic inhalation study (82-4) in the rat. The study duration was

too short and the number of animals used were inadequate to satisfy the Guideline requirement.

Dose/Endpoint for Risk Assessment: NOAEL= 20 mg/$m^3$ (20 µg/L; 5.4 mg/kg/day) based on persistent clinical signs, body weight changes, and gross and histopathological lesions observed at 100 mg/$m^3$ (LOAEL).

Comments about Study/Endpoint: There is residual uncertainty related to exposure from the inhalation route, particularly for acute exposure and for subchronic non-occupational exposure from the off-gasing of MITC. As discussed above, two inhalation toxicity studies are required at this time: 1) an acute inhalation neurotoxicity study including pathological observation of the upper and lower respiratory tract and 2) two-generation reproduction study via the inhalation route with additional measurements to evaluate neurotoxicity.

The results from the 90-day inhalation study with MITC are considered questionable (details can be found in TXR no. 0051394). Specific aspects of this study which increase uncertainty include: body weight changes in untreated vs. sham treated controls; availability of appropriate analytical data to verify chamber concentrations; the duration of exposure was 4 hours instead of the typical 6 hours; and lack of nasal pathological examination for a highly irritating compound.

**a. Dazomet**

Study Selected: Subchronic Inhalation Toxicity-Rat (MITC) § 82-4

MRID No.: 45314802

Executive Summary: See Short- and Intermediate-Term Inhalation Endpoint for MITC.

Dose/Endpoint for Risk Assessment: NOAEL= 20 mg/$m^3$ (20 µg/L; 5.4 mg/kg/day) based on persistent clinical signs, body weight changes, and gross and histopathological lesions observed at 100 mg/$m^3$ (LOAEL).

Comments about Study/Endpoint: See Short- and Intermediate-Term Inhalation Endpoint for MITC.

**8. Long-term (> 6 months) Inhalation Exposure**

**a. Metam Sodium**

Study Selected: 90-Day Inhalation Study with *Metam Sodium* § 82-4

MRID No.: 00162041

Executive Summary: See Short- and Intermediate-Term Inhalation Endpoint

Dose/Endpoint for Risk Assessment: The NOAEL for females is 6.5 mg/m$^3$ (**1.11 mg/kg/day**) of metam sodium (based on Na levels; 0.7 mg/m$^3$ [0.12 mg/kg/day] measured MITC). The LOAEL in females is 45 mg/m$^3$ (7.71 mg/kg/day) of metam sodium (based on Na levels; 2.2 mg/m$^3$ [0.38 mg/kg/day] measured MITC), based on histopathological changes in the naval passages (ie, mucigenic hyperplasia) and changes in clinical chemistry.

Comments about Study/Margins of Exposure: When metam sodium is applied to an agricultural field $CS_2$, $H_2S$, and MIC are formed in addition to MITC. Although the other gases were not measured, due to the rapid degradation of metam sodium, it is assumed that these compounds are also present in the inhalation chamber. Use of this study more accurately reflects the mixture of chemicals that people are actually exposed to, particularly in the field. Finally, the when adjusted for molar equivalents, the NOAEL from the metam sodium inhalation study is protective of the NOAELs identified for use in the inhalation RfC identified in EPA's IRIS database for $CS_2$ and $H_2S$ (19.7 mg/m$^3$ and 1.01 mg/m$^3$, respectively).

**b. MITC**

Study Selected: Long-term inhalation exposure is not expected for MITC; this exposure scenario will not be quantified.

**c. Dazomet**

Study Selected: The HIARC did not select a long-term inhalation endpoint for dazomet. Long term inhalation exposure is not expected considering the use pattern and its stability in the environment.

## 9. Summary of Target Margins of Exposure (MOEs) for Risk Assessment

### a. Metam Sodium

| Target Margins of Exposure for Risk Assessment of Metam Sodium | | | |
|---|---|---|---|
| **Route / Duration** | **Short-Term (1-30 Days)** | **Intermediate-Term (1 - 6 Months)** | **Long-Term (> 6 Months)** |
| **Occupational (Worker) Exposure** | | | |
| **Dermal** | 100 | 100 | 100 |
| **Inhalation** | 100 | 100 | 100 |
| **Residential (Non-Dietary) Exposure** | | | |
| **Oral** | N/A | N/A | N/A |
| **Dermal** | N/A | N/A | N/A |
| **Inhalation** | N/A | N/A | N/A |

**For Occupational exposure:** Target MOEs are based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation)

**For Residential and/or non-occupational exposure:** No residential exposure to metam sodium *per se* is expected.

### b. MITC

| Target Margins of Exposure for Risk Assessment of MITC | | | |
|---|---|---|---|
| **Route / Duration** | **Short-Term (1-30 Days)** | **Intermediate-Term (1 - 6 Months)** | **Long-Term (> 6 Months)** |
| **Occupational (Worker) Exposure** | | | |
| **Dermal** | NA | NA | NA |
| **Inhalation** | 100 | 100 | 100 |
| **Residential (Non-Dietary) Exposure** | | | |
| **Oral** | NA | NA | NA |
| **Dermal** | NA | NA | NA |
| **Inhalation** | 100 | 100 | 100 |

**For Occupational exposure:** For the inhalation route, the target MOE of 100 is based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and

10X for interspecies variation).

**For Residential and/or non-occupational exposure:** For the inhalation route, the target MOE of 100 is based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation).

### c. Dazomet

| Target Margins of Exposure for Risk Assessment of Dazomet | | | |
|---|---|---|---|
| **Route / Duration** | **Short-Term (1-30 Days)** | **Intermediate-Term (1 - 6 Months)** | **Long-Term (> 6 Months)** |
| **Occupational (Worker) Exposure** | | | |
| **Dermal** | 1000 | 100 | N/A |
| **Inhalation** | 100 | 100 | N/A |
| **Residential (Non-Dietary) Exposure** | | | |
| **Oral** | N/A | N/A | N/A |
| **Dermal** | N/A | N/A | N/A |
| **Inhalation** | N/A | N/A | N/A |

**For Occupational exposure:** For the short-term dermal exposure, the target MOE of 1000 is based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation) and a 10X LOAEL to NOAEL factor. For the intermediate-term dermal and for inhalation exposure (all durations), the target MOE of 100 is based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation).

**For Residential and/or non-occupational exposure:** Quantitative risk assessment will not be performed for residential exposure to dazomet.

## IV. CLASSIFICATION OF CARCINOGENIC POTENTIAL

### 1. Metam Sodium

The Health Effects Division Carcinogenicity Peer Review committee (CPRC) met on March 01, 1995 to discuss and evaluate the weight -of-the-evidence on metam sodium with particular reference to its carcinogenic potential. The CPRC concluded that metam sodium should be classified as a Group B2 - probable human carcinogen, based on statistically significant increases in malignant angiosarcomas in both sexes of the CD-1 mouse, supported by a similar tumor type (malignant hemangiosarcomas) in male Wistar rats. The CPRC recommended that for the purpose of risk characterization, a low dose extrapolation model be applied to the animal data for the quantification of human risk

(Q,*) , based on the total incidence of angiosarcomas in male mice, at all sites combined. The most potent unit risk (Q1*) is $1.98x10^{-1}$ in human equivalents converted from animals to humans by use of the 3/4's scaling factor (HED Doc. No. 012954).

**2. Dazomet**

At the March 10, 1993 and on May 26, 1993, meeting the HED Cancer Peer Review Committee (CPRC) classified Dazomet as a **"Group D-** not classifiable as to human carcinogenicity" based on the lack of tumors in male B6C3F1 mice, equivocal evidence for hepatocellular tumors in females, and carcinogenicity and chronic feeding studies in Wistar rats which appeared to be negative for carcinogenicity. The HIARC concurred with the previous classification.

**3. MITC**

The Health Effects Division-RfD/Peer Review Committee met on February 9, 1995 determined that the carcinogenicity studies in both rats (83-2a, MRID No. 00150078) and mice (83-2b, MRID No. 00150075, 00151942) to be unacceptable and not upgradable. In addition to other deficiencies mentioned in the data evaluation records, it was difficult to accurately ascertain the actual doses ingested by the test animals because of the high volatility. Furthermore, the dose levels tested in both studies were inadequate (too low) for carcinogenicity testing in either species. Therefore, the carcinogenic potential of the MITC can not be determined.

The HIARC (May 21, 2002) concurred with the RfD Committee and also concluded that the carcinogenicity studies are unacceptable and can not be upgraded.

The HIARC recommended that in the absence of acceptable negative studies, MITC is assumed $B_2$ - Carcinogen as is metam sodium as a conservative approach. The most potent Q1* $(mg/kg/day)^{-1}$ of metam sodium should be used (with appropriate molar conversion) for the purpose of life time cancer risk assessment. In this case, the most potent unit risk (Q1*)for metam sodium is $1.98x10^{-1}$ in human equivalents converted from animals to humans by use of the 3/4's scaling factor (HED Doc. No. 012954). *Converting this unit risk (Q1*)for metam sodium of $1.98x10^{-1}$ to molar equivalents of MITC, the appropriate cancer unit risk estimate is* ***$3.5x10^{-1}$***.

The approach of performing a low-dose linear cancer risk assessment using the metam sodium data is health protective and conservative in nature. This approach assumes that the statistically significant increases in malignant angiosarcomas and malignant hemangiosarcomas observed in mice and rats, respectively, are *directly* attributable to MITC. It is important to note that in dazomet studies no tumors were observed in male B6C3F1 mice or female and male rats. However, there was equivocal evidence for hepatocellular tumors in females B6C3F1 mice. Metam sodium, MITC, and dazomet have not been reevaluated in accordance with 1999 Draft Carcinogen Risk Assessment Guidelines (July 1999); this reevaluation may be performed in the future.

## V. MUTAGENICITY

### 1. Metam Sodium

The HIARC concluded that there is not a concern for mutagenicity resulting from exposure to metam sodium.

Metam sodium was tested in the unscheduled DNA synthesis using primary rat hepatocytes at concentrations of 0.5, 1.0, 2.5, 5.0, 10.0, 50.0, 100.0, and 250.0 nl/ml. Results of this study showed that metam sodium caused no significant changes in nuclear labeling of primary rat hepatocytes at the concentrations tested (MRID No. 40305601).

Metam sodium was tested in the Rec-Assay with Bacillus subtilis strains H17 and M45 in the absence and presence of metabolic activation (rat liver S-9) at doses up to 150.0 µl/plate. Metam sodium failed to induce differential toxicity in Bacillus subtilis strains H17 and M45 at the concentrations tested (MRID No. 40305602).

Metam sodium was non-mutagenic in the Ames Assay using Salmonella typhimurium strains TA92, TA98, TA100, TA1535, TA1537, and TA1538 in the absence or presence of metabolic activation (rat liver S-9) at doses up to 2500 µg/plate (MRID No. 40305603).

Metam sodium did not induce chromosomal aberration in the In Vitro cytogenic assay using human lymphocytes in the presence or absence of metabolic activation at doses up to 20 µg/ml (MRID No. 40305604).

Metam Sodium was tested for clastogenicity in Chinese hamsters after single oral doses of 150, 300, and 600 mg/kg. Five animals per sex were sacrificed at 6, 24, and 48 hours post-dose for examination of bone marrow cells. At the dose levels tested, metam sodium was not positive for clastogenicity in Chinese hamster bone marrow (MRID No. 40305605).

### 2. MITC

The HIARC concluded that there is a concern for mutagenicity resulting from exposure to MITC. Several mutagenicity studies were available in the database in the categories of gene mutations (84-2a), structural chromosomal aberrations (84-2b), and other genotoxic effects (844).

The structural chromosomal aberration assay in V79 lung cells (84-2b, MRID No. 00150074) was classified as acceptable study. The study was positive in the presence of a metabolic activating system at concentrations as low as 1 µg/ml and in the absence of metabolic activation at concentrations as low as 2.5 µg/ml. The response increased slightly at 12 hours, but clearly increased at 28 hours after the initiation of treatment.

The gene mutation test in the Salmonella and E. coli WP2 uvrA gene mutation assays,(84-2a, MRID No. 41221410) was classified as acceptable study. The study was

negative up to 100 µg/disc, the highest concentration tested.

The unscheduled DNA synthesis (UDS) in primary rat hepatocytes (84-4**,** MRID No. 00150072) for other genotoxic effects was classified as the unacceptable study. The study was negative up to 15.2 µg/ml, the highest dose tested, but no raw data were provided to confirm the results. In addition there were also problems with the positive control.

The V79/hgprt assay for gene mutation (84-2a, MRID No. 00150073) was classified as unacceptable study. The study was negative up to 1 µg/ml without metabolic activation and 2.5 µg/ml with metabolic activation, the highest concentrations tested. It was determined from the limited toxicities that higher concentrations could have been used.

The DNA damage assay in B. subtilis (84-4, MRID No. 41221410) was classified as unacceptable study. The study was negative up to 2000 µg/disc, the highest concentration tested. However, no toxicity was observed at the highest dose tested, no precautions were taken against compound loss (volatile compound), only single plates were used, and the chemical was not tested under activated conditions.

The sister chromatid exchange assay in V79 cells (84-2b, MRID #41221412) was classified as unacceptable study. The test was negative up to 3.5 µg/ml without metabolic activation and 5 µg/ml with metabolic activation, the highest concentrations used; but higher concentrations could have been used since it did not attain appropriate toxicity levels.

The HIARC recommended the in vivo cytogenetics assay, as a follow-up to the positive in-vitro results. Also a repeat of the unscheduled DNA synthesis assay is necessary to satisfy the data gap in other genotoxic effects category.

**3. Dazomet**

The HIARC concluded that there is not a concern for mutagenicity resulting from exposure to dazomet.

Several studies submitted by the Registrant(s) were unacceptable guideline studies. The CPRC in 1993 concluded that dazomet has genotoxic capability. In *in vitro* studies, dazomet is not mutagenic in the Ames test (bacteria, unacceptable studies), non mutagenic in the Rec assay (bacteria) and negative for inducing DNA damage/repair, and does not cause unscheduled DNA damage in primary rat hepatocytes. It was negative in *in vivo* bone marrow cytogenetic assay, micronucleus assay and in *in vitro* cytogenetic assay with human lymphocytes. It was positive in mammalian cells in culture gene mutation in Chinese hamster ovary (CHO) cells.

*Salmonella typhimurium* reverse gene mutation assay: The test is negative in *S. typhimurium* strains TA1535, TA1537, TA 1538, TA98 and TA100 to 1000 µg/plate, in the presence and absence of S9 activation. The study is classified as unacceptable and does not satisfies the requirements for FIFRA Test Guideline 84-2 (MRID No. 00131910). The CPRC considered that the results were unacceptable because a positive

overall response compared to controls occurred.

Rec assay with *Bacillus subtilis*: The test is negative in *Bacillus subtilis* at doses up to 10,000 µg/plate, in the presence and absence of S9 activation. The study is classified as acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 (MRID No. 41482301).

Mouse Lymphoma: dazomet was found to increase mutation frequency at the thymidine kinase locus in the absence of metabolic activation. In addition, increase of structural chromosome aberration occurred at dose level of 4 and 5 µg/ml in the absence of metabolic activation. No increase in sister chromatid exchange was observed in the absence or presence of metabolic activation and increase in mutation frequency at the thymidine kinase locus was observed in the presence of metabolic activation. The study is classified as acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 (MRID No. 00131912).

*In vitro* CHO cells Assay: dazomet was positive for induction of forward mutation at the HGPRT locus in Chinese hamster ovary (CHO) cells exposed to nonactivated and activated at doses ranging from 0.01 to 0.464 pg/mL. The study is classified as acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 (MRID No. 41497901).

Sex-Linked Recessive Lethal Test in *Drosophila:* Dazomet was inactive in the production of sex-linked recessive lethals in *Drosophila melanogaster* at doses up to 0.05 mg/mL. The study is classified as acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 (Accession No. 251207, Study No. T-10012.).

*In vivo* mammalian cytogenetic assay: The test is negative in male Chinese hamsters receiving single oral gavage doses of dazomet up to 100 mg/kg. The study is classified as acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for *in vivo* mammalian cytogenetic data (MRID No. 41497902).

Mouse micronucleus assay: The test is negative in male and female NMRI mice receiving single oral gavage doses of dazomet up to 180 mg/kg. There was no indication of an effect on the target cell. The study is classified as acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for a mouse micronucleus assay (MRID No. 41497903).

*In vitro* mammalian cell cytogenetic assay: Dazomet was negative for the inducing chromosome aberration in human lymphocytes at dose levels up to 0.05 µg/mL -S9 or 25 µg/mL +S9. The study is classified as acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for a *in vitro* mammalian cell cytogenetic data (MRID No. 41482302).

*In vivo* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes: The test is negative for the induction of unscheduled DNA synthesis (UDS) in hepatocytes recovered from rats administered single oral gavage doses Dazomet from 37.5-300

mg/kg. The study is classified as acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for a UDS assay (MRID No. 41482303).

## VI. HAZARD CHARACTERIZATION

Metam sodium, metam potassium, and dazomet are converted to MITC in the environment, particularly soil after application. It is MITC that performs the fumigating activity. Metam sodium, metam potassium, and dazomet are efficiently converted to MITC *in vivo*. MITC is primarily an irritating compound that produces non-specific systemic effects in oral toxicity studies such as changes in body weight, food consumption, and hematological parameters. The mode of toxic action for MITC is not known at this time. Although toxicological databases for metam sodium and dazomet are complete for risk assessment purposes, the toxicological database for MITC is not complete. Many toxicological studies via the oral route with MITC do not meet the guideline requirements, primarily due to problems surrounding the volatility of MITC and inadequate characterization of exposure concentrations or doses. Some of the data gaps are being filled through bridging with the toxicology databases of metam sodium and dazomet. Specifically, for evaluating the sensitivity and susceptibility of infants and children, the HIARC has previously concluded that oral dazomet developmental and reproductive toxicity studies can serve as a surrogate for MITC. Because of inadequate dosing in the oral chronic/carcinogenicity studies in mice and rats, the oral MITC studies are considered inadequate for evaluating carcinogenic potential. The Q-1* for metam sodium (adjusted by molar conversion to MITC) has been used for quantitative cancer risk assessment to MITC.

Pharmacokinetic and metabolism studies in rats for dazomet, metam sodium, and MITC were submitted to support metabolism for metam sodium. Each compound was tested at two dose levels. It was shown that all three were excreted mainly in urine with urinary recoveries over 168 hours of 63-65% for dazomet, 37-58% for metam sodium, and 84-87% for MITC. Excretion via the feces was low–usually ranging from 1.5% to 3.3%. Three different compounds (MITC, $CO_2$, $COS/CS_2$ ) were found to be excreted via the lungs. Total excretion of the 3 products of the lungs over a 73 hour collection period were about 35% and 50% for metam sodium, 22% and 28% for dazomet, and 22% and 9% for MITC at low and high doses, respectively. There were no differences between males and females in amounts excreted via the three excretion routes. Tissue retention at 168 hours was about 2% for all 3 compounds at both dose levels. Total recoveries, including the percentage of the doses excreted and that remaining in the tissues combined after 168 hours, ranged from 92.6% to 106%, indicating virtually complete absorption from the GI tract. By the first 24 hours, 85% or more of each of the 3 compounds at both dose levels had been excreted. All three compounds were also rapidly absorbed from the GI tract with plasma tmax between 0.25 and 1.0 hours. However, plasma half-lives after 24 hours were long, ranging from around 60 to 74 hours for all three compounds. Tissue and plasma levels at all time periods, and plasma AUCs were consistently higher in females than in males by a substantial amount. The tissue with the highest uptake for all three compounds was the thyroid gland. High uptake were also seen by the liver, kidneys, and lung, with the lowest level in testes, brain and eyes. Metabolic profiles detected in urine, liver, and kidneys were basically similar for the three compounds but there were some differences, mainly quantitative in nature.

There is remarkable similarity in the oral doses causing similar toxic effects for metam sodium,

dazomet, and MITC, particularly at low to moderate doses. Specifically, reduced body weight gain and food consumption in addition to changes in hematological parameters were observed at low doses in oral toxicity studies with rats, mice, rabbits, and dogs. Effects on the liver have been noted in dogs at doses with similar molar levels. Reduced motor activity has been noted at all dose levels in oral acute neurotoxicity testing in studies with metam sodium and dazomet. In oral developmental toxicity studies with MITC, dazomet, and metam sodium, effects such as fetal weight decrements, reduced ossification of various skeletal structures, and increased incidence of resorptions have been noted at similar molar dose levels. There is no quantitative susceptibility observed in the oral developmental and reproductive toxicity studies with metam sodium, MITC, or dazomet. All of the developmental NOAELs are equal to or larger than the NOAELs for maternal toxicity. There is, however, qualitative susceptibility in two rabbit developmental studies with dazomet and two rat developmental toxicity studies with metam sodium. In these studies, increased incidence of resorptions were noted at a dose that resulted in maternal body weight gain decreases. At higher doses levels of metam sodium, the neurotoxic effects from the *in vivo* production of $CS_2$ begin to manifest. Specifically, incidence of meningocele has been noted following oral administration of metam sodium in two developmental studies in rat and one developmental study in rabbits. There were no neuropathological changes noted in the oral acute and subchronic neurotoxicity studies with metam sodium and dazomet, however, the doses used in the metam sodium subchronic toxicity study may not be sufficiently high to detect these effects. There is some limited evidence that MITC may cause immunotoxicity at high doses (Kiel et al., 1996). There is no evidence of endocrine disruption in the database. The systemic effects following dermal exposure to metam sodium at this time are not known; the existing dermal study does not take adequate precautions for the volatilization of MITC. Therefore, HED has elected to use oral studies and route to route extrapolation using a dermal absorption factor in its risk assessment.

Relating to the inhalation toxicity with these pesticides, two subchronic inhalation studies in MITC, one subchronic inhalation studies in metam sodium, and no inhalation studies in dazomet are available at this time. There is existing uncertainty related to the adverse effects following exposure to MITC via the inhalation route, particularly for acute or single day exposures. Histological changes consistent with a highly irritating compound were observed in the 28-day study with MITC and also the 90-day study with metam sodium. In the 90-day inhalation study with MITC, negative histopathological findings are questionable because of several reasons such as lack of nasal pathology and poor analytical data. As suggested by results of the human eye irritation with MITC and oral acute neurotoxicity studies with metam sodium and dazomet, single inhalation exposures may potentially result in adverse effects. An acute inhalation neurotoxicity study in MITC with additional measurements to characterize the complete respiratory tract is required at this time. There are no studies available for evaluating the route specific effects of MITC in the young, therefore an inhalation reproductive toxicity study is required at this time. Additional justification for this study come from inhalation developmental studies with MIC, a photolysis degradate of MITC, (Schwetz et al, 1987; Shilohi et al, 1986; Varma, 1987; Varma et al., 1987) which report effects such as pup death and survivability.

There are several toxicologically notable metabolites/degradates of metam sodium, metam potassium, MITC, and dazomet. Methyl isocyanate (MIC) is a photolysis degradate of the MITC. MIC is a toxic and irritating compound which has been detected in ambient air in parts of California. Following soil application of metam sodium, both $CS_2$ and $H_2S$ can be formed; the

relative amounts depend on the pH of the soil. Following oral exposure to metam sodium, rats metabolize approximately 20-25% of the dose (on a molar basis) to $CS_2$. $CS_2$ is a neurotoxic agent known to cause a variety of effects such as neuropathology and changes in sensory conduction velocity and peroneal motor conduction velocity. Exposure to $H_2S$ at low levels in humans can result in eye injury, headaches, nausea, and insomnia. Comprehensive reviews of the toxicological profiles of $CS_2$ and $H_2S$ are available on EPA's IRIS website and are briefly summarized in the Revised Toxicological Chapter for Metam Sodium and MITC (TXR no. 0052455).

In acute toxicity testing, MITC is Acute Toxicity Category II for the oral and inhalation routes and Category I for the dermal route. MITC also causes skin and eye irritation (Acute Toxicity Category I) and is a sensitizer in guinea pigs. Eye irritation and odor threshold for MITC has been evaluated in humans (MRID 44400401). Metam sodium and dazomet are relatively less acutely toxic compared to MITC. Metam sodium is of low toxicity (Acute Toxicity Category III) in acute toxicity studies by the oral, dermal, and inhalation routes. Metam sodium is not a skin and eye irritant (Category III and IV, respectively) and is negative for skin sensitization in guinea pigs.

Metam sodium was negative in several mutagenicity assays (including the chromosomal aberration, clastogenicity, Salmonella assay, an unscheduled DNA synthesis ). Carcinogenic potential was evidenced by statistically significant increases in malignant angiosarcomas in both sexes of the CD-1 mouse and also supported by a similar tumor type (malignant hemangiosarcomas) in male Wistar rats. Metam sodium is classified as a 'probable human carcinogen.' For the purpose of risk characterization, a low dose extrapolation model be applied to the animal data for the quantification of human risk (Q,*) , based on the total incidence of angiosarcomas in male mice, at all sites combined.

Several of the MITC mutagenicity studies are considered unacceptable. MITC was positive in the structural chromosomal aberration assay in V79 lung cells. The carcinogenicity studies in both rats and mice are considered unacceptable based on deficiencies related to the actual doses ingested by the test animals because of the high volatility and instability of the test material. Therefore, the carcinogenic potential of the MITC can not be determined. In the absence of appropriate data, the MITC is assumed to have the same carcinogenic potential as metam sodium.

In *in vitro* studies, dazomet is not mutagenic in the Ames test (bacteria, unacceptable studies), non mutagenic in the Rec assay (bacteria) and negative for inducing DNA damage/repair, and does not cause unscheduled DNA damage in primary rat hepatocytes. It was negative in *in vivo* bone marrow cytogenetic assay, micronucleus assay and in *in vitro* cytogenetic assay with human lymphocytes. It was positive in mammalian cells in culture gene mutation in Chinese hamster ovary (CHO) cells. Carcinogenicity and chronic feeding studies in Wistar rats appeared to be negative for carcinogenicity at doses up to 16.36 mg/kg/day in males and 21.54 mg/kg/day in females. There was lack of tumors in male B6C3F1 mice at doses up to 69.9 mg/kg/day and equivocal evidence for hepatocellular tumors in females at doses up to 21.54 mg/kg/day. Dazomet is currently classified as Group D-not classifiable as to human carcinogenicity.

## VII. DATA GAPS/REQUIREMENTS

### 1. Metam Sodium/Metam Potassium

At present time, the HIARC has not identified any data gaps for metam sodium or metam potassium.

### 2. MITC

The database MITC is incomplete for pesticidal uses of MITC *per se*, and additional data requirements may be imposed. The HIARC has identified following studies on MITC as the data gaps:

1. Acute neurotoxicity study in rat via inhalation with pathological evaluation of the complete respiratory tract.
2. Two generation reproduction study in rat via inhalation with pathological evaluation of the complete respiratory tract. This study should also include a subchronic neurotoxicity component with functional battery and motor activity measurements using the F0 animals. If the F1 animals exhibit developmental neurotoxicity then the F2 generation should be evaluated for the standard developmental neurotoxicity parameters.
3. In vivo cytogenetic assay
4. Repeat of the unscheduled DNA synthesis assay

### 3. Dazomet

At present time, the HIARC has not identified any data gaps for dazomet.

## VIII. ACUTE TOXICITY

### 1. Metam Sodium

**Acute Toxicity of Metam Sodium (P. C. Code 039003)**

| Guideline No. | Study Type | MRIDs # | Results | Toxicity Category |
|---|---|---|---|---|
| 81-1 | Acute Oral-Rat | 41277002 | $LD_{50}$ =7 80 mg/kg (male rats)<br>845 mg/kg (female rats) | III |
| 81-2 | Acute Dermal-Rat | 41277003 | $LD_{50}$ = >2020 mg/kg | III |
| 81-3 | Acute Inhalation-Rat | 41277004 | $LC_{50}$ = 2.27 mg/L | III |
| 81-4 | Primary Eye Irritation | 41277005 | No corneal/iris involvement; all irritation was absent by 7 days | III |
| 81-5 | Primary Skin Irritation-Rabbit | 41277006 | non-irritating to the skin of male rabbits | IV |
| 81-6 | Dermal Sensitization | 41277007 | Negative in guinea pigs | |
| 81-8 | Acute Neurotoxicity-Rat | 42977801 and 42977802 | The LOAEL of 22 mg/kg is based on reduced ambulatory and total motor activity observed in male & female rats. The NOAEL < 22 mg/kg and was not achieved in this study | |

## 2. MITC

**Acute Toxicity of Methyl Isothiocyanate (PC Code 068103 )**

| Guideline No. | Study Type | MRID #(S). | Results | Toxicity Category |
|---|---|---|---|---|
| 81-1 | Acute Oral-Rat | 00162331 | $LD_{50}$ = 82 mg/kg ♂<br>55 mg/kg ♀ | II |
| 81-2 | Acute Dermal-Rat | 00162330<br>42443501 | $LD_{50}$ = 136-436 mg/kg ♂<br>181 mg/kg ♀ | I |
| 81-3 | Acute Inhalation-Rat | 45919410 | $LC_{50}$ = 0.54 mg/L | II |
| 81-4 | Primary Eye Irritation | 00162328 | corrosion of the cornea and conjuctivae | I |
| 81-5 | Primary Skin Irritation | 00162329 | all animals died within one hour | I |
| 81-6 | Dermal Sensitization | 459194101 | positive for sensitization in guinea pig | |

## 3. Dazomet

**Acute Toxicity of Dazomet (PC Code 035602)**

| Guideline No. | Study Type | MRID #(S) | Results | Toxicity Category |
|---|---|---|---|---|
| 81-1 | Acute Oral | 00132468 | $LD_{50}$ = 596 mg/kg ♂<br>$LD_{50}$ = 415 mg/kg ♀<br>$LD_{50}$ = 519 mg/kg (combined) | II<br>based on female value |
| 81-2 | Acute Dermal-Rats | 42328802 | $LD_{50}$ = >2000 mg/kg | III |
| 81-3 | Acute Inhalation | 41563003 | $LC_{50}$ =>8.40 mg/L ♂<br>7.29 mg/L ♀ | IV |
| 81-4 | Primary Eye Irritation | 41563002 | slight to well defined conjunctival redness and chemosis. Returned to normal within 72 hours | III |
| 81-5 | Primary Skin Irritation | 42328801 | non-irritating to the skin of male rabbits | IV |
| 81-6 | Dermal Sensitization | 47014505 and 44031801 | Not a sensitizer | N/A |

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## IX. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

### 1. Metam Sodium/Metam Potassium

Summary of Toxicology Endpoint Selection for
*Metam Sodium (PC Code 39003)* and *Metam Potassium (PC Code 39002)*

| Exposure Scenario | Dose Used in Risk Assessment | Uncertainty Factors and Level of Concern for Risk Assessment | Study and Toxicologial Effects |
|---|---|---|---|
| **Acute Dietary** general population including infants and children | Acute dietary endpoints were not selected since the use-pattern does not indicate potential for dietary exposure. | | |
| **Chronic Dietary** all populations | Chronic dietary endpoints were not selectedsince the use-pattern does not indicate potential for dietary exposure. | | |
| **Incidental Oral**<br><br>Short- and Intermediate-Term (1 - 30 Days; 1-6 Months)<br><br>Residential Only | Short- and intermediate term incidental oral endpoints were not selected since the use-pattern does not indicate potential for this exposure scenario. | | |
| **Dermal**<br>Short-Term (1 - 30 days)<br><br>Residential and Occupational | Maternal NOAEL[a,d]= 4.22 mg/kg/day<br><br>Dermal absorption factor = 2.5% | **Residential** LOC for MOE[b] = N/A[e]<br><br>**Occupational** = LOC[c] for MOE = 100 | **Developmental toxicity in rat (MRID 41577101)**<br>LOAEL[f] = 16.88 mg/kg/day based on reduced body weight gain and decreased food efficiency in maternal rats |
| **Dermal**<br>Intermediate-Term (1 - 6 Months)<br><br>Residential and Occupational | Oral NOAEL[a]= 0.1 mg/kg/day<br><br>Dermal absorption factor = 2.5% | **Residential** LOC for MOE = N/A<br><br>**Occupational** = LOC for MOE = 100 | **Chronic toxicity in dog (MRID 43275801)**<br>LOAEL = 1 mg/kg/day based on increased ALT and microscopic changes in the liver in females. |

| Exposure Scenario | Dose Used in Risk Assessment | Uncertainty Factors and Level of Concern for Risk Assessment | Study and Toxicologial Effects |
|---|---|---|---|
| **Dermal**<br>Long-Term<br>(> 6 Months)<br><br>Residential and Occupational | Oral NOAEL[a]= 0.1 mg/kg/day<br><br>Dermal absorption factor = 2.5% | **Residential** LOC for<br>MOE = N/A<br><br>**Occupational** = LOC for MOE = 100 | **Chronic toxicity in dog (MRID 43275801)**<br>LOAEL = 1 mg/kg/day based on based on increased ALT and microscopic changes in the liver in females. |
| **Inhalation**<br>Short-, Intermediate, and Long-Term<br>(1 - 30 days, 1-6 Months, and > 6 Months)<br><br>Residential and Occupational | Inhalation NOAEL= 6.5 $mg/m^3$ (1.11 mg/kg/day) | **Residential** LOC for<br>MOE = N/A<br><br>**Occupational** = LOC for MOE = 100 | **90-day inhalation study (MRID 00162041)**<br>LOAEL =45 $mg/m^3$ (7.71 mg/kg/day) in females based on histopathological changes in the naval passages (ie, mucigenic hyperplasia) and changes in clinical chemistry. |
| **Cancer** | **Classification:** Probable human carcinogen (B2)<br>**Q1*** =$1.98x10^{-1}$ in human equivalents converted from animals | | |

a Since an oral NOAEL was selected, a dermal absorption factor of 2.5% should be used in route-to-route extrapolation.; b Margin of Exposure (MOE) = 100 [10x for interspecies extrapolation and 10x for intraspecies variations.]; c LOC = level of concern; d NOAEL = no observed adverse effect level; e NA = Not Applicable; f LOAEL = lowest observed adverse effect level.

## 2. MITC

Summary of Toxicology Endpoint Selection for Methyl isothiocyanate (PC Code 068103)

| Exposure Scenario | Dose Used in Risk Assessment | Uncertainty Factors and Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|
| **Acute Dietary** General population including infants and children | Dietary exposure is not expected for MITC at present time. | | |
| **Chronic Dietary** (All populations) | Dietary exposure is not expected for MITC at present time. | | |
| **Incidental Oral** Short-Term (1 - 30 Days) | Incidental oral exposure is not expected for MITC | | |
| **Incidental Oral** Intermediate-Term (1 - 6 Months) | Incidental oral exposure is not expected for MITC | | |
| **Dermal** Short-Term (1 - 30 days), Intermediate-Term (1 - 6 Months) Long-Term (> 6 Months) | No dermal hazard via typical dermal contact with MITC is expected. Unprotected skin could exposed to MITC vapor; however this exposure can not, at this time, be quantified. | | |
| **Inhalation** Short-Term (1 - 30 days) Intermediate-Term (1 - 6 Months) Long-Term (>6 Months) | Inhalation NOAEL[c]= 5.4 mg/kg/day | **Residential** LOC for MOE = 100[a] **Occupational** LOC[b] for MOE = 100[a] | **Subchronic inhalation toxicity- rat with *MITC* (MRID 45314802)** LOAEL[d] = 27 mg/kg/day based on persistent clinical signs, body weight changes, and gross and histopathological lesions |
| **Cancer** | **Classification:** Based on lack of appropriate data, assumed to be probable human carcinogen (B2) from metam sodium Q1* =3.54 x$10^{-1}$ in human equivalents converted from animals | | |

a Margin of Exposure (MOE) or Uncertainty Factors (UF) = 100 [10x for interspecies extrapolation, 10x for intraspecies variations.]; b LOC = level of concern; c NOAEL = no observed adverse effect level; d LOAEL = lowest observed adverse effect level.

## 3. Dazomet

Summary of Toxicology Endpoint Selection for Dazomet (PC Code 035602)

| Exposure Scenario | Dose Used in Risk Assessment | Uncertainty Factors and Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|
| **Acute Dietary** (General population including infants and children) | Acute dietary endpoints were not selected since the use-pattern does not indicate potential for dietary exposure. | | |
| **Chronic Dietary** (All populations) | Chronic dietary endpoints were not selected since the use-pattern does not indicate potential for dietary exposure. | | |
| **Incidental Oral**<br><br>Short-Term (1 - 30 Days)<br><br>Residential Only | Incidental oral exposure is not expected for dazomet. | | |
| **Incidental Oral**<br><br>Intermediate-Term (1 - 6 Months)<br><br>Residential Only | Incidental oral exposure is not expected for dazomet. | | |
| **Dermal**<br>Short-Term (1 - 30 days)<br><br>Residential and Occupational | Oral LOAEL[a]= 15 mg/kg/day | **Residential**<br>LOC[c] for MOE = N/A<br><br>**Occupational**<br>LOC for MOE = 1000[d] | **Acute neurotoxicity study (MRID 43465302)**<br>LOAEL[f] = 15 mg/kg in females (6.75 mg/kg MITC equivalents; decreased motor activity) based on neurobehavioral effects FOB findings and reduced number of rearings**.** |
| **Dermal**<br>Intermediate-Term (1 - 6 months)<br><br>Residential and Occupational | Oral NOAEL[a,e]= 1.5 | **Residential**<br>LOC for MOE = N/A[h]<br><br>**Occupational**<br>LOC for MOE = 100[g] | **Subchronic toxicity- feeding rats (MRID 41865502)**<br>LOAEL = 4.5 mg/kg/day based on increased liver weight, liver:body weight ratio and pronounced foci of fatty degeneration in the liver |

| Exposure Scenario | Dose Used in Risk Assessment | Uncertainty Factors and Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|
| **Dermal**<br>Long-Term<br>(> 6 Months)<br><br>Residential and Occupational | Long-Term exposure via the dermal route is not expected considering the use pattern and its stability in the environment. | | |
| **Inhalation**<br>Short-Term<br>(1 - 30 days)<br>Intermediate-Term<br>(1 - 6 Months) | Inhalation NOAEL= 5.4 mg/kg/day | **Residential**<br>LOC for MOE = N/A<br><br>**Occupational**<br>LOC for MOE = 100[g] | **Subchronic inhalation toxicity- rat with MITC (MRID 45314802)**<br>LOAEL = 27 mg/kg/day based on based on persistent clinical signs, body weight changes, and gross and histopathological lesions |
| **Inhalation**<br>Long-Term<br>(>6 Months)<br><br>Residential and Occupational | Long term inhalation exposure is not expected considering the use pattern and its stability in the environment. | | |
| **Cancer** | **Classification: Not classifiable as human carcinogen.** | | |

a Use 4.5% dermal absorption to convert oral dose to dermal equivalent; c Level of Concern = LOC; d Margin of Exposure (MOE) = 1000 [10x for interspecies extrapolation, 10x for intraspecies variations, 10x NOAEL to LOAEL factor]; e NOAEL = no observed adverse effect level; f LOAEL = lowest observed adverse effect level; g 100 [10x for interspecies extrapolation, 10x for intraspecies variations.]; h. N/A= Not applicable,

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